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Crosstalk between G-protein and Ca2+ pathways switches intracellular cAMP levels

Valeyev N., Heslop-Harrison P., Postlethwaite I., Gizatullina A., Kotov N., Bates D.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Cyclic adenosine monophosphate and cyclic guanosine monophosphate are universal intracellular messengers whose concentrations are regulated by molecular networks comprised of different isoforms of the synthases adenylate cyclase or guanylate cyclase and the phosphodiesterases which degrade these compounds. In this paper, we employ a systems biology approach to develop mathematical models of these networks that, for the first time, take into account the different biochemical properties of the isoforms involved. To investigate the mechanisms underlying the joint regulation of cAMP and cGMP, we apply our models to analyse the regulation of cilia beat frequency in Paramecium by Ca2+. Based on our analysis of these models, we propose that the diversity of isoform combinations that occurs in living cells provides an explanation for the huge variety of intracellular processes that are dependent on these networks. The inclusion of both G-protein receptor and Ca 2+-dependent regulation of AC in our models allows us to propose a new explanation for the switching properties of G-protein subunits involved in nucleotide regulation. Analysis of the models suggests that, depending on whether the G-protein subunit is bound to AC, Ca2+ can either activate or inhibit AC in a concentration-dependent manner. The resulting analysis provides an explanation for previous experimental results that showed that alterations in Ca2+ concentrations can either increase or decrease cilia beat frequency over particular Ca2+ concentration ranges. © The Royal Society of Chemistry.

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